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New Colistin Population Pharmacokinetic Data in Critically Ill Patients Suggesting an Alternative Loading Dose Rationale

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Colistin is an old antibiotic that has recently gained a considerable renewal of interest as the last-line defense therapy against multidrug-resistant Gram-negative bacteria. It is administered as colistin methanesulfonate (CMS), an inactive prodrug, and it was shown that due to slow CMS conversion, colistin plasma concentrations increase very slowly after treatment initiation, which constitutes the rationale for a loading dose in critically ill patients. However, faster CMS conversion was observed in healthy volunteers but using a different CMS brand, which may also have a major impact on colistin pharmacokinetics. Seventy-three critically ill patients not undergoing dialysis received multiple doses of CMS. The CMS concentrations were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS), and a pharmacokinetic analysis was conducted using a population approach. We confirmed that CMS renal clearance and colistin concentrations at steady state are mostly governed by creatinine clearance, but we predict a typical maximum concentration of drug in serum (C_{max}) of colistin close to 2 mg/liter, occurring 3 h after an initial dose of 2 million international units (MIU) of CMS. Accordingly, the estimated colistin half-life ($t_{1/2}$) was relatively short (3.1 h), with rapid attainment of steady state. Our results are only partially consistent with other recently published results. We confirm that the CMS maintenance dose should be adjusted according to renal function in critically ill patients. However, much higher than expected colistin concentrations were observed after the initial CMS dose, with rapid steady-state achievement. These discrepancies challenge the pharmacokinetic rationale for a loading dose, which may still be appropriate for rapid bacterial eradication and an improved clinical cure rate.

Colistin is an antibiotic that has reemerged because of the increase of bacterial resistance among life-threatening Gram-negative pathogens (1). It is administered intravenously as a prodrug, colistin methanesulfonate (CMS), which is converted within the body into the active moiety. It was shown that colistin concentrations increase slowly after CMS administration in critically ill patients and that it takes 2 days to reach steady state, suggesting the benefits of treatment initiation with a loading dose (2). This front-loading strategy is now well accepted to increase efficacy and avoid the development of resistances (3–5). However, this slow appearance of colistin was not observed in healthy volunteers (6). The objective of this study was therefore to reassess colistin pharmacokinetics (PK) in critically ill patients using the same methodology, including CMS brand, as that for healthy volunteers.

MATERIALS AND METHODS

Study design. The study was approved by the ethics committee of the principal investigator hospital. It was an open-label study conducted in 9 sites in France between May 2009 and December 2011. The eligible patients were hospitalized in the intensive care unit (ICU), were >18 years of age, and received CMS for treatment of Gram-negative infection. Patients who received renal replacement therapy were excluded from the analysis. Each patient received CMS (Colimycine; Sanofi-Aventis) as a 1-h infusion every 8 or 12 h, according to dosage regimens freely chosen by physicians. Colimycine was purchased from Sanofi-Aventis (Paris, France) as a dry powder and reconstituted in 50 ml of saline just before dosing. Patients could also receive CMS in aerosol form. The doses were expressed in millions of international units (MIU), with 1 MIU approximately equivalent to 30 mg of colistin-based activity (CBA) or 80 mg of CMS sulfate (7). Blood samples were collected after the initial CMS administration for the assay of CMS and colistin in plasma, typically at 10 to 30 min after starting infusion, 5 min before the end of infusion, 2 to 3 h after starting initiation dose, and 5 min before starting the next one. Other samples were collected occasionally after the subsequent administrations, 5 min before starting (trough), and 5 min before ending (peak) CMS infusions. The blood samples were rapidly centrifuged, and the plasma was separated and kept frozen before analysis, as previously described (6, 8, 9). Urine samples were collected in two centers. The plasma and urine samples were kept frozen at 20°C before being assayed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (8).

Pharmacokinetic modeling. CMS and colistin concentrations were analyzed simultaneously using nonlinear mixed-effects regression (population approach) with the Monolix 4.1 software (10). A previously used model was initially considered (6). Further model selection (1 versus 2 compartments) was done using a likelihood ratio test. However, no distribution phase was observed, and a one-compartment model was used for CMS, since statistically, its likelihood was not different from that of a two-compartment model ($P < 0.05$). It was assumed that only CMS was excreted in urine (6, 11). The differences in the molecular masses between CMS (1,632 g/mol) and colistin (1,167 g/mol) were considered for biotransformation rate calculation. Plasma concentrations below the limit of quantification were handled by the Beal M3 method (12).

To characterize the contribution of aerosol cotreatment on plasma

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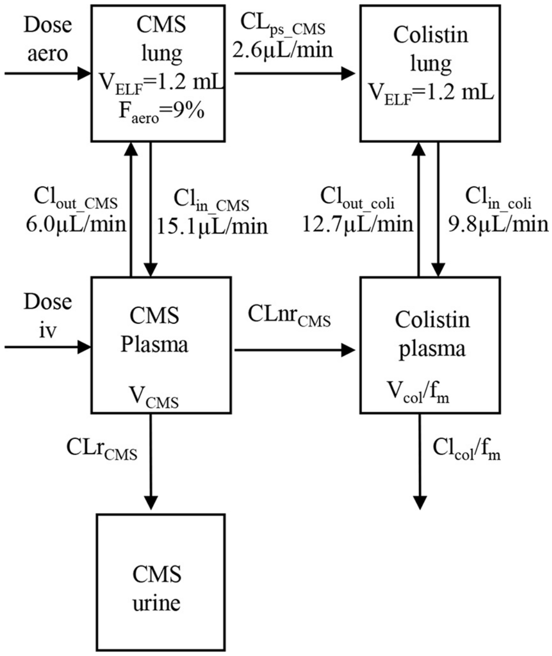

FIG 1 Structural pharmacokinetic model: V_{ELF}, volume of distribution in lung compartment; F_{aero}, fraction of the aerosol dose that reaches systemic circulation; CL_{out_CMS}, clearance of CMS from the central to lung compartments; CL_{in_CMS}, clearance of CMS from the lung to central compartments; CL_{ps_CMS}, presystemic clearance of CMS biotransformation in colistin; CL_{out_coli}, clearance of colistin from central to lung compartments; CL_{in_coli}, clearance of colistin from lung to central compartments; V_{CMS}, volume of distribution of CMS; CL_{RCMS}, renal clearance of CMS; CL_{NRCMS}, nonrenal clearance of CMS; V_{col}, volume of distribution of colistin; CL_{col}, total clearance of colistin; f_m, fraction of the CMS dose not excreted unchanged that is converted into colistin.

CMS and colistin concentrations, relevant pharmacokinetic parameters values obtained from an accompanying study (M. Boisson, M. Jacobs, N. Grégoire, P. Gobin, S. Marchand, O. Mimoz, and W. Couet [13]) in separate (n = 12) critical care patients, using CMS and colistin concentrations measured in plasma and bronchoalveolar samples collected after separate administrations of CMS intravenously or as an aerosol, were fixed to independent estimates, reported in Fig. 1. Using these parameter values, only 9% of the dose would reach the systemic circulation after aerosolization.

The interindividual and intraindividual (interoccasion) variabilities of the PK parameters were modeled, assuming a log-normal distribution. The residual variability was modeled as proportional for CMS plasma concentrations and combined (additive plus proportional) for colistin plasma and CMS urine concentrations.

The effects of various covariates on the model parameters were tested: gender, age, body weight, simplified acute physiology score (SAPS II) (14) on admission, body temperature, leukocyte count, platelet count, creatinine clearance (calculated with the Cockcroft and Gault formula and capped at 130 ml/min, as previously described [15]), plasma urea, diuresis, plasma creatinine, urinary pH, blood pH, hemoglobinemia, plasma protein concentration, albumin, PaO_2 (partial pressure of oxygen), FiO_2 (fraction of inspired oxygen), bicarbonates, prothrombin ratio, hematocrit, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase.

The covariate models were parameterized as follows: $\theta_i = \theta_{pop} (COV_i/COV_{median})^{\beta}$, where θ_i is the individual PK parameter, θ_{pop} is the typical value of the PK parameter, COV_i is the individual covariate value, COV_{median} is the population median of the covariate, and β is the power coefficient describing the change in parameter. Covariate selection was done in two steps. In a first step, the relationships between the individual covariate values and individual parameter estimates were assessed through linear regression for continuous covariates and χ^2 tests for categorical covariates. In the second step, all relationships with a P value of $<$0.05 were included in the model, and stepwise backwards selection was then performed based on the Wald test, with a threshold of a P value of $<$0.05.

The final model was assessed by an inspection of the observed versus predicted concentrations, residual variability, precision of parameter estimates, visual predictive check (VPC), and normalized prediction distribution errors (NPDE).

Evaluation of renal toxicity. Renal toxicity was evaluated at the end of treatment using the RIFLE nomenclature, which differentiates 5 increasing grades of renal insufficiency: risk, injury, failure, loss, and end stage (16).

RESULTS

Patient characteristics, treatments, and toxicity. The demographic characteristics of the 73 critically ill patients enrolled (43 males and 30 females) are presented in Table 1. Most (n = 71) patients received CMS intravenously, three times daily (TID). The median first dose was 2 MIU, but 16 patients received a 7.5- to 9-MIU loading dose, and the median maintenance dose was 6 MIU/day. In 29 patients, CMS was also aerosolized (1 to 2 MIU 1 or 3 times daily). At the end of treatment, 5 cases of renal toxicity were considered potentially attributed to CMS treatment, 3 were classified as risk, and 2 were classified as injury.

CMS and colistin pharmacokinetics. Between 2 and 20 plasma samples were collected per patient at various times during

TABLE 1 Patient characteristics[a]

Characteristic (n = 73)[b]	Median (range)
Age (yr)	62 (18–91)
Wt (kg)	76 (40–175)
SAPS II score	42 (9–101)
Body temp (°C)	37.7 (34.1–39.8)
Leukocyte count (×1,000/mm^3)	12.1 (1.6–39.4)
Platelet count (×1,000/mm^3)	311 (16–862)
Creatinine clearance (ml/min)	86 (14–368)
Plasma urea (mmol/liter)	8.8 (2.2–73)
Daily diurese (liter)	1.7 (0.0–7.3)
Plasma creatinine (μmol/liter)	90 (18–481)
Urinary pH	6 (5–8)
Blood pH	7.5 (7.1–7.7)
Hemoglobin (g/dl)	8.7 (5.8–13.2)
Plasma proteins (g/liter)	59 (10–84)
Albumin (g/liter)	21 (7–38)
PaO_2 (mm Hg)	103 (31–495)
FiO_2 (%)	40 (21–500)
Bicarbonates (meq/liter)	26.5 (10–106)
Prothrombin ratio (%)	73 (16–114)
Hematocrit (%)	27 (18–40)
Total bilirubin (mg/liter)	8 (2–299)
AST (IU/liter)	35 (5–535)
ALT (IU/liter)	38 (8–902)
Gamma-GT (IU/liter)	96 (13–593)
Alkaline phosphatases (IU/liter)	149 (28–1,364)
CMS first dose (MIU)	2.0 (0.3–9)
CMS maintenance dose (MIU/day)	6.0 (0.9–9)

[a] Of the 73 patients, 30 (41%) were female, and 29 (40%) underwent aerosol therapy.
[b] AST, aspartate aminotransferase; ALT, alanine aminotransferase; gamma-GT, gamma-glutamyltransferase.

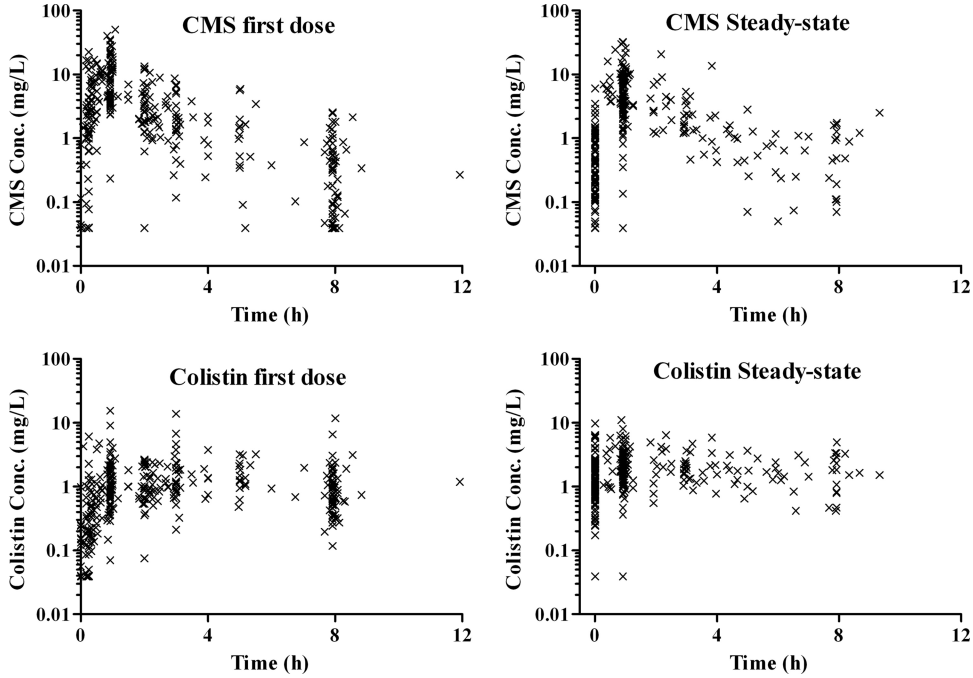

FIG 2 CMS and colistin plasma concentrations (Conc.) observed (x) in 73 critically ill patients after first CMS dose and at steady state.

treatment (total number, 634) at various times after treatment initiation and on 1 to 5 distinct occasions. Urine samples ($n = 38$) were collected over 8-h dosing intervals in 23 patients. In plasma, 108 CMS concentrations and 71 colistin concentrations were below the limit of quantification.

The plasma concentrations of CMS and colistin after the first CMS administration and at steady state are presented in Fig. 2. The corresponding PK parameter estimates are shown in Table 2.

The CMS elimination half-life was short (typical value, 1.6 h), with most (61%, according to the model) of the dose excreted unchanged in urine. CMS renal clearance (CL_{RCMS}) was related to creatinine clearance (CL_{CR}) as shown in equation 1 (Eq 1):

$$CL_{RCMS} = 68.5 \times \left(\frac{Cr_{CL}}{85}\right)^{0.85} \tag{1}$$

The CMS volume of distribution (V_{CMS}) was influenced by body weight, according to

$$V_{CMS} = 15.7 \times \left(\frac{\text{Weight}}{70}\right)^{1.1} \tag{2}$$

The colistin elimination half-life was longer than that of CMS (typical value, 3.1 h). Its volume of distribution was independent of body weight but was found to decrease when body temperature increased:

$$V_{col}/f_m = 10.2 \times \left(\frac{\text{Body temperature}}{37}\right)^{-8.7} \tag{3}$$

Colistin clearance was not related to creatinine clearance but to plasma urea as follows:

$$CL_{col}/f_m = 37.7 \times \left(\frac{\text{Plasma urea}}{10}\right)^{-0.22} \tag{4}$$

The inter- and intraindividual variabilities in both the CMS and colistin PK parameters were relatively large in spite of the covariates included in the model. The inclusion of CL_{CR}, weight, and body temperature decreased the interindividual variability of CL_{RCMS}, V_{CMS}, and V_{col}/f_m (V_{col}, volume of distribution of colistin; f_m, fraction of the CMS dose not excreted unchanged that is converted into colistin) by 30%, 4%, and 1% (in absolute value), respectively, whereas the inclusion of plasma urea increased the interindividual variability of CL_{col}/f_m by 12%. The effect of plasma urea was conserved in the final model, according to the statistical

TABLE 2 Population pharmacokinetic parameters

Drug and parameter[a]	Typical value (RSE%)[b]	Interindividual variability CV% (RSE%)[c]	Intraindividual variability CV% (RSE%)
CMS			
V_{CMS} (liters)	15.7 (7)	44 (14)	32 (16)
β_wt on V_{CMS}	1.1 (26)		
CL_{RCMS} (ml/min)	68.5 (12)	72 (11)	34 (15)
β_CL_{CR} on CL_{RCMS}	0.85 (19)		
CL_{NRCMS} (ml/min)	43.7 (11)	42 (18)	16 (63)
Colistin			
V_{col}/f_m (liters)	10.2 (16)	81 (15)	51 (23)
β_T° on V_{col}	−8.7 (41)		
CL_{col}/f_m (ml/min)	37.7 (10)	37 (15)	29 (16)
β_urea on CL_{col}	−0.22 (40)		

[a] V_{CMS}, volume of distribution of CMS; β, power coefficients describing the change in parameter as follows: $V_{CMS} = 15.7 \times (\text{weight}/70)^{\beta\_\text{wt}}$, $CL_{RCMS} = 68.5 \times (CL_{CR/85})^{\beta\_CLCR}$, $V_{col}/f_m = 10.2 \times (\text{body temperature}/37)^{\beta\_T°}$, $CL_{col}/f_m = 37.7 \times (\text{plasma urea}/10)^{\beta\_\text{Urea}}$; CL_{RCMS}, renal clearance of CMS; CL_{CR}, creatinine clearance; CL_{NRCMS}, nonrenal clearance of CMS; V_{col}, volume of distribution of colistin; f_m, fraction of the CMS dose not excreted unchanged that is converted into colistin; CL_{col}, total clearance of colistin.

[b] RSE, relative standard error (expressed as a percentage).

[c] CV, coefficient of variation.

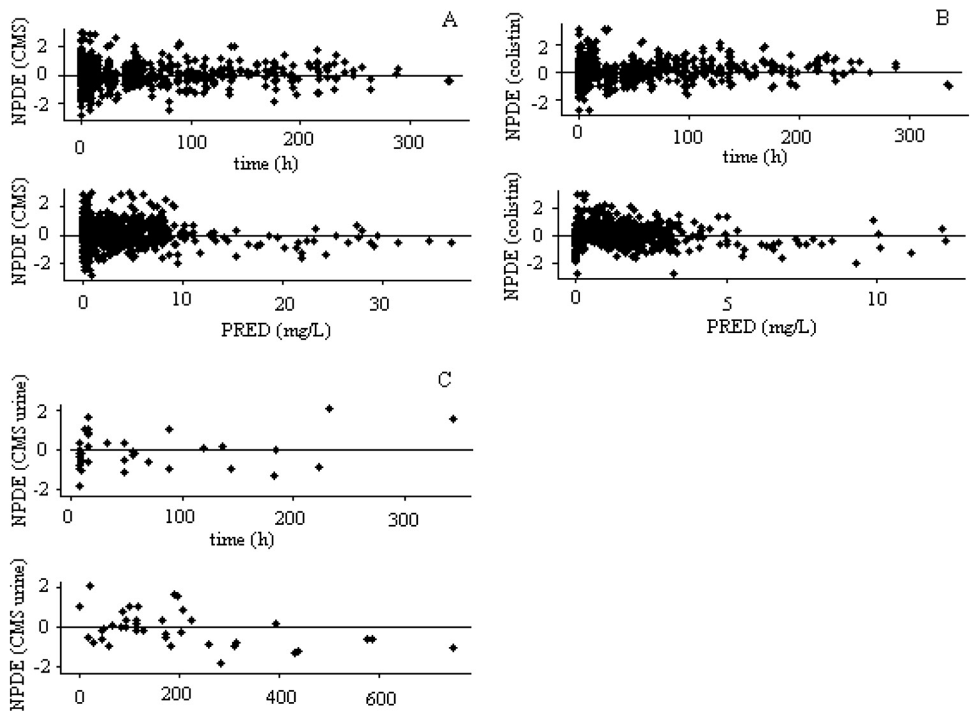

FIG 3 Normalized prediction distribution errors (NPDE) as a function of time and typical predictions (PRED) for CMS plasma concentrations (A), colistin plasma concentrations (B), and CMS urine concentrations (C).

criteria (improvement in the −2LL and value of the Wald test, $P = 0.01$) and because it decreased the intraindividual variability of CL_{col}/f_m by 6%.

Goodness of fit. Goodness-of-fit data plots were satisfactory with unbiased individual fits, except for a few urine sample data (data not shown), probably due to inaccurate quantitative collection. The coefficients of determination (r^2) for the observed versus individually fitted CMS and colistin plasma concentrations were 0.66 and 0.89, respectively. The NPDE values were <3, and no obvious bias was observed versus time or typical predictions (Fig. 3). The residual variability (Table 3) was low for colistin plasma concentrations (19% proportional and 0.16 μg/ml additive), moderate for CMS concentrations in urine (47% proportional and 12.2 μg/ml additive), and relatively high for CMS concentrations in plasma (56%). The precision with the parameter estimates (expressed as relative standard error, Table 2) was good (<63%).

DISCUSSION

Precise comparisons between studies are difficult because of differences in study design and patient characteristics. Plachouras et al. (2) measured CMS and colistin plasma concentrations from 8 samples collected after the first dose and at steady state in 18 patients with preserved renal function who received a CMS maintenance dose of 3 MIU every 8 h (q8h). Garonzik et al. (17) collected 8 plasma samples also but only at steady state and in a larger number of patients ($n = 105$) with various degrees of renal failure, including some undergoing hemodialysis, and accordingly, various dosing regimens. We used a sparse sampling strategy with a smaller number of samples collected after the first dose and at steady state but with intermediate samples. Our patients presented various degrees of renal failure and therefore, various dosing treatments were used.

The CMS elimination half-life in our patients was short (typical value, 1.6 h). Yet although the decay of CMS concentrations with time appeared to be monoexponential, a previously reported rapid initial distribution phase (2, 17) may not have been observable due to the lack of early data points. Consequently, the CMS elimination half-life and volume of distribution reported in this study may be underestimated and should not be directly compared with previously reported values.

Our predictions of CMS concentrations at the end of a 2-MIU infusion are close to 6.5 μg/ml, which is consistent with those of Garonzik et al. (17), when according to Plachouras et al. (2), the CMS peak should be close to only 3.5 mg/liter. The volume of distribution mostly determines this peak value (18). We confirmed that V_{CMS} is proportional to body weight (17) but is quite low, since according to Eq 3, it should increase from 12.5 liters to 24.9 liters when body weight increases from 50 kg to 100 kg.

Garonzik et al. (17) reported that the CL_{RCMS} was virtually identical to CL_{CR}, and we found a slightly different relationship (see Eq 1), since for patients with CL_{CR} values of 25, 50, and 120 ml/min, our formula predicts CL_{RCMS} values of 24, 44, and 92 ml/min, respectively, whereas the formula of Garonzik et al. (17)

TABLE 3 Residual errors for CMS and colistin plasma and urine

Residual error type	Proportional CV% (RSE%)[a]	Additive (%) (μg/ml)
CMS plasma	56 (4)	
Colistin plasma	19 (9)	0.16 (10)
Urine	47 (21)	12.2 (56)

[a] CV, coefficient of variation; RSE, relative standard error.

TABLE 4 Pharmacokinetic parameters derived for a typical Plachouras patient[a] across studies

Parameter[b]	Plachouras et al. (2)	Garonzik et al. (17)	Present study
CMS			
CL_{CMS} (ml/min)	228	115.7	110.1
V_{CMS} (liters)	13.5	15.9	18.2[c]
Vp_{CMS} (liters)	28.9	18.7	
CL_{RCMS} (ml/min)		84.1	66.4
$t_{1/2}$ (h)	2.3	4.5	1.9
Colistin			
$1 - f_e$		0.27	0.40
$CL_{col}/f_{m.col}$ (ml/min)	151.5	207.1	94.3
$V_{col}/f_{m.col}$ (liters)	189	164.8	25.7
$t_{1/2}$ (h)	14.4	9.2	3.2

[a] With a CL_{CR} of 82 ml/min and body weight of 80 kg.
[b] CL_{CMS}, total clearance of CMS; V_{CMS}, volume of distribution of central compartment for CMS; Vp_{CMS}, volume of distribution of peripheral compartment for CMS; CL_{RCMS}, renal clearance of CMS; $t_{1/2}$, terminal half-life; $1 - f_e$, fraction of CMS not excreted unchanged in urine; CL_{col}, apparent clearance of colistin; V_{col}, apparent volume of distribution of colistin; $f_{m.col}$, fraction of CMS converted in colistin.
[c] Volume for a one-compartment model.

predicts values of 26, 51, and 123 ml/min, respectively. Although the Cockroft and Gault formula may not provide an accurate estimate of the glomerular filtration rate (GFR) in critically ill patients (19), the values obtained with the modification of diet in renal disease (MDRD) formula were not much different (R^2 = 0.84). Interestingly, when CL_{CR} equals 130 ml/min, as estimated in our healthy volunteers, Eq 1 predicts CL_{RCMS} to be 101 ml/min, which is almost identical to the value actually estimated in these volunteers (103 ml/min) (6). Although Garonzik et al. (17) did not gather information from urine sample analysis, their CL_{RCMS} estimate is consistent with ours. Noticeably, our estimate of CMS nonrenal clearance (CL_{NRCMS}) in critically ill patients was 44 ml/min on average, which is almost identical to the value (45 ml/min) previously reported in healthy volunteers (6).

As opposed to CMS, alterations of colistin disposition in critically ill patients are difficult to assess, because its PK parameters cannot be calculated without estimating the fraction of the CMS dose eventually converted into colistin, which would require direct administration of colistin (11). Furthermore, this parameter raises a terminology issue requiring clarification. It was previously referred to by Plachouras et al. (2) and by Couet et al. (6) as f_m. However, according to Garonzik et al. (17), f_m corresponds to the fraction of the CMS dose not excreted unchanged that is converted into colistin (17). For clarification, we decided to keep the Garonzik et al. terminology and introduce $f_{m.col}$ as a new term to characterize the fraction of the CMS dose eventually converted into colistin, with the relationship between $f_{m.col}$ and f_m given as

$$f_{m.col} = f_m(1 - f_e) = \frac{f_m \times CL_{NRCMS}}{CL_{NRCMS} + CL_{RCMS}} \quad (5)$$

It was initially suggested (1) that the fraction of the CMS dose not excreted unchanged in urine ($1 - f_e$) (f_e, fraction excreted in urine) was totally converted into colistin ($f_{m.col}$ = 1). This assumption was previously made by Plachouras et al. (2) and by Couet et al. (6), but it was not retained in the present study, since f_m is likely to be <1 (17, 18). Although difficult to estimate, it is important to understand how $f_{m.col}$ may vary between subjects and what would be the consequences for colistin concentrations. Because the typical CL_{NRCMS} value was virtually identical in critically ill patients (44 ml/min) and healthy volunteers (45 ml/min), $f_{m.col}$ should increase when renal function decreases, with a value at 32% when CL_{CR} is 120 ml/min and 80% when CL_{CR} is 10 ml/min. This explains why the average colistin concentrations at steady state are expected to increase when CL_{CR} decreases, although the renal excretion of colistin is negligible (11).

In order to allow comparisons between the studies, the apparent volume ($V_{col}/f_{m.col}$) and clearance ($CL_{col}/f_{m.col}$) terms are reported in Table 4. However, because these apparent parameter values are difficult to interpret, it is more informative to compare their effect on colistin concentrations in a "typical Plachouras patient" (i.e., one with a body weight of 80 kg and CL_{CR} of 82 ml/min) treated with 3 MIU of CMS q8h. The profile corresponding to a typical healthy volunteer receiving 3 MIU of CMS is also presented in Fig. 4 for comparison purposes. Although these typical profiles fail to reflect the important interpatient variability, which is a major characteristic of colistin pharmacokinetics, they illustrate a major discrepancy between studies conducted at early times after the initial CMS dose, since Plachouras et al. (2) predicted a typical peak concentration of colistin of 0.6 mg/liter and occurring at 8 h, whereas we predicted a 3-mg/liter (5-fold higher) peak occurring after 3 h in a typical Plachouras patient. This difference is a major concern, since the slow increase in colistin reported by Plachouras et al. (2) constitutes the rationale for a loading dose. Although blood samples were rapidly centrifuged and plasma was quickly frozen, it could be argued that even limited uncontrolled CMS degradation within the blood or plasma samples might lead to artificially high colistin concentrations at early sampling times, since CMS concentrations are much higher than colistin concentrations. Yet, due to its short elimination half-life (typical value, 1.6 h), most of the CMS was cleared at 8 h postdose, so CMS degradation cannot account for high colistin concentrations at that time. After normalization for dose, we observed much higher colistin concentrations at trough than the average value predicted by Plachouras et al. (2), as illustrated in Fig. 4. The use of different brands of CMS, Colimycine (Sanofi-Aventis) in the present study versus colistin (Norma) in the Plachouras et al. study

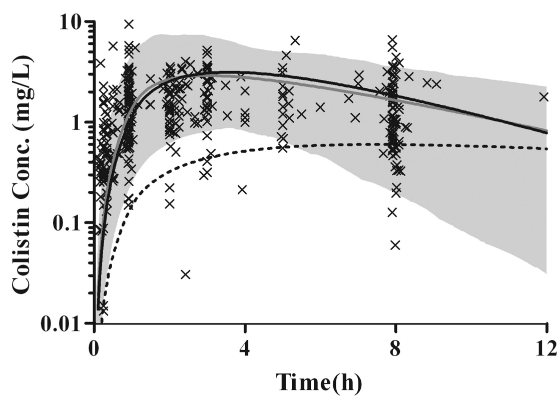

FIG 4 Typical colistin plasma profiles predicted from present results (full black line), along with 90% confidence intervals (gray shaded area), from those of a healthy volunteer (full gray line) (6) and the work of Plachouras et al. (dashed black line) (2) after a single 3-MIU CMS dose administered as a 60-min infusion. The colistin plasma concentrations (Conc.) observed in the present study and normalized to a 3-MIU dose are also shown (X).

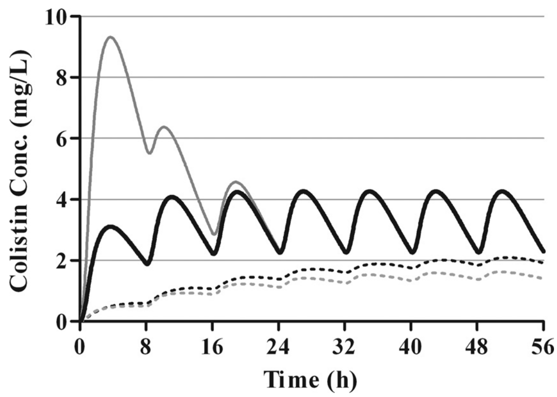

FIG 5 Colistin concentrations (Conc.) following a 3-MIU dose of CMS infused over 60 min every 8 h in a typical Plachouras patient (i.e., CL_{CR}, 82 ml/min, and body weight, 80 kg), predicted without a loading dose from our results (black solid line) and those of Plachouras et al. (black dashed line) (2) and Garonzik et al. (gray dashed line) (17) and with a 9-MIU loading dose from our results (gray solid line).

(2), might contribute to these discrepancies, since major PK differences have recently been observed between various brands of CMS in rats (20). Interestingly, profiles corresponding to critically ill patients and healthy volunteers receiving 3 MIU of the same CMS brand (Colimycine; Sanofi-Aventis) are virtually superimposed.

As opposed to the initial concentrations and apart from larger fluctuations in colistin concentrations between two consecutive administrations at steady state due to a shorter half-life, our predicted average colistin concentrations at steady state are not much different from those predicted by Plachouras et al. (2) or Garonzik et al. (17), which are only 35% and 55% lower than ours, respectively (Fig. 5).

The major between-study discrepancies in early colistin concentrations following the initial CMS dose are essentially accounted for by differences in $V_{col}/f_{m.col}$ terms (Table 4), since we report a typical value for this parameter approximately 7-fold lower than that of Plachouras et al. (26.2 liters versus 189 liters, respectively) (2), whereas the relatively limited difference between the predicted average colistin concentrations at steady state (3.4 μg/ml versus 2.2 μg/ml for Plachouras et al.) reflects the relatively consistent estimates of $CL_{col}/f_{m.col}$. The differences or similarities between the apparent volume and clearance terms are difficult to interpret due to the unknown $f_{m.col}$ value. However, this term cancels out when expressing the elimination half-life, which may then be compared between studies. The half-lives reported by Plachouras et al. (2), Garonzik et al. (17), and us for a typical Plachouras patient are 14.4 h, 9.0 h, and 3.1 h, respectively (Table 4). Unfortunately, the colistin elimination phase is difficult to observe after CMS administration every 8 h, with a peak occurring at about 4 h postdose. But the relatively long half-life ($t_{1/2}$) reported by Plachouras et al. (2) corresponds to the fact that it takes about 48 h before reaching steady state, and it constitutes the rationale for a loading dose. Our shorter $t_{1/2}$ estimate suggests that steady state should be reached within a few hours after dosing. Accordingly, a 2-μg/ml concentration of colistin, corresponding to the European Committee on Antimicrobial Susceptibility (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) breakpoints for susceptibility, should be obtained after 2 h on average in our patients, compared with the estimate of 48 h, as suggested by Plachouras et al. (2). Therefore, from a PK point of view, our results do not support the use of a loading dose (Fig. 5), but because 9-MIU loading doses of CMS are now used with no apparent signs of toxicity, including the few patients who received this loading dose in the present study, it may still be of interest to use a high initial dose in treatment in order to eradicate bacteria more aggressively (15, 21). Dalfino et al. (22) showed a high clinical cure rate (82.1%) and low renal toxicity after a 9-MIU loading dose and a 9-MIU daily maintenance dose (4.5 MIU every 12 h [q12h]) (22, 23). Integrated PK-pharmacodynamics (PD) modeling as done by Mohamed et al. (15) is now required to confirm the pharmacodynamic rationale for CMS treatment initiation with a loading dose.

The results of this new multicenter population pharmacokinetics study of CMS and colistin in critically ill patients are partially consistent with those recently published (2, 17). It is confirmed that CMS maintenance doses should be adjusted according to renal function. However, major discrepancies were observed between studies after the initial CMS dose, possibly due to differences in CMS brands. This observation challenges the pharmacokinetic rationale for a loading dose. However, since higher-than-expected colistin concentrations may be achieved after an initial 9-MIU dose of CMS, with no apparent major side effects, this front loading strategy may be valuable in the eradication of difficult-to-treat infections in critically ill patients.

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